PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32366A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/02710	International filing date *(day/month/year)* 14.03.2003	Priority date *(day/month/year)* 15.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D239/48		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.07.2003	09.03.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Menegaki, F Telephone No. +49 89 2399-8277

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02710

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-34 as originally filed

Claims, Numbers

1-9 received on 03.12.2003 with letter of 29.11.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 5-9

   because:

   ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations

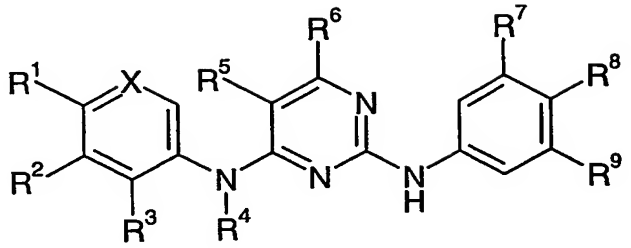
   see separate sheet

(III)
Claims 5,6,7,9 are directed to a method of treatment of the human/animal body and therefore no preliminary examination is required (Rule 67.1(iv) PCT).
Moreover, it is noted by the IPEA that for the assessment of Claims 5,6,7,9 on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, e.g., does not recognize the subject-matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

(V)
Novelty: The new definition of Claim 1, by incorporating original Claim 2, can be regarded as novel if said definition is defined as a disclaimer, i.e., "...provided that, (not "wherein"), **one** of $R^{1,2,3}$ is $-CON(R^{10})R^{11}$ or $-SO_2N(R^{10})R^{11}$. By incorporating said disclaimer, the requirements of Art.33(2) PCT appear to be fulfilled.
Inventive step: The problem underlying the invention is considered to be the provision of novel 2,4-arylamino substituted pyrimidine compounds having the activity described on p.26,27, namely antitumour, antiinflammatory, antiasthmatic, against autoimmune diseases etc., which was generally known from doc.(D1), (D3), (D4) and (D8). The activity as referred to in the Applicant's letter of 29/11/03 was partly known and partly related to a new pharmakokinetic action leading to a similar therapeutic effect, and is therefore regarded as belonging to the tyrosine kinase inhibiting activity in general, which was known to exist for numerous, originally novelty destroying, prior art compounds in the above documents, now excluded by introducing the disclaimer into new Claim 1. In this connection reference is made, in particular to compounds 106, 122 of (D1). Moreover, the specific definitions of $R^{1,2,3}$ as defined in the disclaimer were known from (D4), in particular Ex.76-78, 85-87, 97-105, wherein pyridine analogue compounds with similar activity were disclosed. Therefore, it is considered that the skilled man would have expected the present compounds to possess similar qualitative properties, and in view of lack of any unexpected advantage over nearest prior art compounds of (D1)/(D4), the requirements of Art.33(3) PCT do not appear to be fulfilled.

Claims:

1. A compound of formula I



(I)

wherein

X is $=CR^0-$ or $=N-$;

each of R^0, R^1, R^2, R^3 and R^4 independently is hydrogen; hydroxy; C_1-C_8alkyl; C_2-C_8alkenyl; C_3-C_8cycloalkyl; C_3-C_8cycloalkyl-C_1-C_8alkyl; hydroxyC_1-C_8alkyl; C_1-C_8alkoxyC_1-C_8alkyl; hydroxyC_1-C_8alkoxyC_1-C_8alkyl; arylC_1-C_8alkyl which optionally may be substituted on the ring by hydroxy, C_1-C_8alkoxy, carboxy or C_1-C_8alkoxycarbonyl;

or R^3 and R^4 form together with the nitrogen and carbon atoms to which they are attached a 5 to 10 membered heterocyclic ring and comprising additionally 1, 2 or 3 heteroatoms selected from N, O and S;

or each of R^1, R^2 and R^3, independently, is halogen; halo-C_1-C_8alkyl; C_1-C_8alkoxy; halo-C_1-C_8alkoxy; hydroxyC_1-C_8alkoxy; C_1-C_8alkoxyC_1-C_8alkoxy; aryl; arylC_1-C_8alkoxy; heteroaryl; heteroaryl-C_1-C_4alkyl; 5 to 10 membered heterocyclic ring; nitro; carboxy; C_2-C_8alkoxycarbonyl; C_2-C_8alkylcarbonyl; -N(C_1-C_8alkyl)C(O) C_1-C_8alkyl; -N(R^{10})R^{11}; -CON(R^{10})R^{11}; -SO_2N(R^{10})R^{11}; or -C_1-C_4-alkylene-SO_2N(R^{10})R^{11}; wherein each of R^{10} and R^{11} independently is hydrogen; hydroxy; C_1-C_8alkyl; C_2-C_8alkenyl; C_3-C_8cycloalkyl; C_3-C_8cycloalkyl-C_1-C_8alkyl; C_1-C_8alkoxyC_1-C_8alkyl; hydroxyC_1-C_8alkoxyC_1-C_8alkyl; hydroxyC_1-C_8alkyl; (C_1-C_8alkyl)-carbonyl; arylC_1-C_8alkyl which optionally may be substituted on the ring by hydroxy, C_1-C_8alkoxy, carboxy or C_2-C_8alkoxycarbonyl; or 5 to 10 membered heterocyclic ring;

or R^1 and R^2 form together with the C-atoms to which they are attached aryl or a 5 to 10 membered heteroaryl residue comprising one or two heteroatoms selected from N, O and S; or

each of R^5 and R^6 independently is hydrogen; halogen; cyano; C_1-C_8alkyl; halo-C_1-C_8alkyl; C_2-C_8alkenyl; C_2-C_8alkynyl; C_3-C_8cycloalkyl; C_3-C_8cycloalkylC_1-C_8alkyl; C_5-C_{10}arylC_1-C_8alkyl;

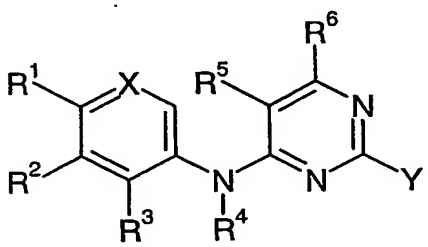
each of R^7, R^8 and R^9 is independently hydrogen; hydroxy; C_1-C_8alkyl; C_2-C_8alkenyl; halo-C_1-C_8alkyl; C_1-C_8alkoxy; C_3-C_8cycloalkyl; C_3-C_8cycloalkylC_1-C_8alkyl; arylC_1-C_8alkyl;

-Y-R^{12} wherein Y is a direct bond or O and R^{12} is a substituted or unsubstituted 5, 6 or 7 membered heterocyclic ring comprising 1, 2 or 3 heteroatoms selected from N, O and S; carboxy; (C_1-C_8alkoxy)-carbonyl; -N(C_{1-8}alkyl)-CO-$NR^{10}R^{11}$; -$CONR^{10}R^{11}$; -N(R^{10})(R^{11}); -$SO_2N(R^{10})R^{11}$; R^7 and R^8 or R^8 and R^9, respectively form together with the carbon atoms to which they are attached, a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from N, O and S; or a 5 or 6 membered carbocyclic ring.

in free form or salt form.

2. A compound according to claim 1 wherein at most one of R^1, R^2 or R^3 is -CON(R^{10})R^{11}; or -$SO_2N(R^{10})R^{11}$.

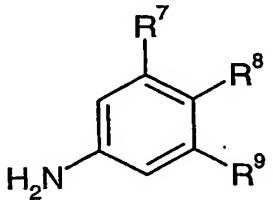
3. A process for the production of a compound of formula I according to claim 1, comprising the steps of reacting a compound of formula II



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in claim 1, and Y is a leaving group;

with a compound of formula III



(III)

wherein R^7, R^8 and R^9 are as defined in claim 1;

and recovering the resulting compound of formula I in free form or in salt form, and, where required, converting the compound of formula I obtained in free form into the desired salt form, or vice versa.

4. A compound according to claim 1 in free form or in pharmaceutically acceptable salt form, for use as a pharmaceutical.

5. A pharmaceutical composition comprising a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers or diluents therefor.

6. The use of a compound of formula I according to claim 1 in free form or in pharmaceutically acceptable salt form, as a pharmaceutical for the treatment or prevention of a disease or condition in which ZAP-70, FAK and/or Syk tyrosine kinase activation plays a role or is implicated.

7. The use of a compound of formula I according to claim 1 in free form or in pharmaceutically disease or condition in which ZAP-70, FAK and/or Syk tyrosine kinase activation plays a role or is implicated.

8. A combination which comprises (a) a therapeutically effective amount of a ZAP-70, FAK and/or Syk inhibitor and (b) a second drug substance.

9. A method for treating or preventing a disease or condition in which ZAP-70, FAK and/or Syk tyrosine inhibitor activation plays a role or is implicated, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof.

10. A method for treating or preventing a disease or condition in which ZAP-70, FAK and/or Syk tyrosine inhibitor activation plays a role or is implicated, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a ZAP-70, FAK and/or Syk inhibitor in combination with a second drug substance.